8, 11 and 14 and hence are also rejected based on the independent claims. Applicants herein remove the offending language to recite merely "an esterified hyaluronic acid." It is believed that the rejection is moot in view of the amendment.

Claims 1-6

The Examiner rejects claims 1-6 under 35 U.S.C. 112, second paragraph, as unclear. Claims 1 and 4 recite a substratum with a layer of fibroblasts which is "at least sub-confluent." A substratum with no cells is at least sub-confluent. According to the Examiner, it is unclear whether fibroblasts are, or are not, growing on the biosynthetic substratum. Claims 2, 3, 5 and 6 are rejected based upon the limitation of the claims from which they depend. Applicants herein remove the offending language to recite that the dermal fibroblast layer "begins to proliferate." Support for the amendment may be found in the specification at page 4, lines 14-28, among other places.

Claims 2, 3, 5, 6, 9, 10, 12 and 13

The Examiner rejects claims 2, 3, 5, 6, 9, 10, 12 and 13 under 35 U.S.C. 112, second paragraph, as unclear. Claims 2, 5, 9 and 12 recite an allogenic dermal fibroblast. Claims 3, 6, 10, and 13 recite an autologous dermal fibroblast. According to the Examiner, it is unclear to what or whom the cells are autologous or allogenic. Applicants herein add the language "to the keratinocytes" in each of the claims rejected to specify what is meant by the terms.

Claims 4-6

The Examiner rejects claims 4-6 under 35 U.S.C. 112, second paragraph, as unclear. Claim 4 recites "... a first basal side..." and subsequently "... a second upper side." Claims 5 and 6 depend from claim 4. According to the Examiner, it is unclear from the claim how many basal sides and /or upper sides constitute the biosynthetic substratum. Applicants herein remove the recitations of "first" and "second" to clarify the claim language.

Claims 11-13

The Examiner rejects claims 11-13 under 35 U.S.C. 112, second paragraph, as unclear. Claim 11 recites "... a first basal side..." and subsequently "... a second upper side." Claims 12 and 13 depend from claim 11. According to the Examiner, it is unclear from the claim how many

basal sides and /or upper sides constitute the said biosynthetic substratum. Applicants herein remove the recitations of "first" and "second" to clarify the claim language.

Claim 15

The Examiner rejects claim 15 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 15 recites "...allowing a sufficient time to form a vascularized wound bed..." According to the Examiner, it is unclear from the claim what a period is a "sufficient time" for vascularization. Applicants herein delete the recitation "sufficient time" so that the claim language reads "allowing a vascularized wound bed to form" thereby obviating the rejection.

Rejection under 35 USC § 102

The Examiner rejects claims 1 and 8 under 35 U.S.C. 102(b) as anticipated by Della Valle *et al.*, U.S. Patent 5,658,331. Claim 1 is drawn to a method of cultivating graftable skin involving the co-culture of fibroblasts and keratinocytes on a biosynthetic substrate wherein the substrate is a benzyl derivative of hyaluronic acid. Claim 8 is drawn to a graftable skin material produced by the method of claim 1.

The Examiner says that co-culturing keratinocytes with fibroblasts to achieve better keratinocyte growth is well established in the art. The Examiner adds that the use of hyaluronic acid (HA) and specific derivatives of hyaluronic acid for the culturing of keratinocytes is also well established in the art. Allegedly, biosynthetic substrates comprising benzyl esterified derivatives of hyaluronic acid were commercially available at the time of applicants filing date and have been specifically marketed for the use of culturing keratinocytes for the production of graftable skin.

The Examiner says that Della Valle *et al.* disclose a bio-compatible artificial skin and a method for producing the same employing a benzyl-esterified HA membrane. The method involves the deposition of fibroblasts on the HA membrane followed by the addition of keratinocytes and subsequent co-culturing of the keratinocytes and fibroblasts. (citing columns 4 and 5, Example 3).

Applicants submit that the use of irradiated or mitomycin C-treated 3T3 cells as a feeder layer for the cultivation of human keratinocytes on tissue culture dishes has been widely applied for burn treatment although the exact role(s) of the 3T3 cell is not yet clear. 3T3 cells are derived from mouse fibroblasts. Tremendous effort has been made to replace the 3T3 cells with human fibroblasts because 3T3 cells are xenogenic. However, ***there have been no reports about the use of human cells, either autologous or allogenic dermal fibroblasts, as a feeder layer for cultivation of keratinocytes on culture dishes or on other substratum such as those of the present invention including LaserskinTM.*** Human dermal fibroblasts were first seeded on a three-dimensional scaffold made of benzyl ester of hyaluronan (HyaffTM, Fidia) as reported by Zacchi *et al., Biomed Mater Res* 1998; 40:187-194. The HyaffTM was biologically modified as a dermal equivalent. An epidermal equivalent was prepared by plating keratinocytes on the LaserskinTM, which was previously seeded with non-proliferative 3T3 cells. When the keratinocytes became confluent, the cultured LaserskinTM was placed on top of HyaffTM and was further cultured for another 15 days. ***This is quite different from the present invention where an epidermal equivalent of keratinocytes plated on a substratum such as LaserskinTM which has been pre-seeded with proliferating human dermal fibroblasts.*** Moreover, HyaffTM is structurally different from the substratum of the present invention. Therefore, Della Valle *et al.* do not teach or suggest the presently claimed invention.

Rejection under 35 USC § 103

In considering obviousness, the Examiner must cite prior art which discloses each element of the claim unless the element would be obvious to one of skill in the art. The Examiner must also provide reasons or motivation for one of skill to combine the prior art references to carry out the claimed method and demonstrate that one of ordinary skill would have had a reasonable expectation of success in attempting to carry out the method. *In re Vaeck*, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991). There must be objective evidence of all three elements. *In re Fine*, 5 U.S.P.Q. 2d 1596 (Fed. Cir. 1988).

Della Valle *et al.* in view of Hansbrough *et al.*

The Examiner rejects claims 2, 3, 9 and 10 under 35 U.S.C. 103(a) as being unpatentable over Della Valle *et al.* in view of Hansbrough *et al.*, JAMA(1989) 262: 21225-2130. Claims 2 and 3 are drawn to methods of cultivating a graftable skin material wherein said skin comprises autologous or allogenic fibroblasts. Claims 9 and 10 are drawn to graftable skin material wherein the graftable skin comprises autologous or allogenic fibroblasts. Della Valle *et al.* teach the use of a benzyl esterified biosynthetic substratum incorporating keratinocytes seeded over a layer of mouse 3T3 fibroblasts for the production of graftable skin. The Examiner admits that Della Valle *et al.* do not teach the use of allogenic or autologous fibroblasts in the method. However, according to the Examiner, the utility of using autologous or allogenic cells for the purpose of grafting would be prima facie obvious to one skilled in the art based on the fact that these types of cells are best suited for the avoidance of immune response and hence graft rejection. The use of allogenic cells, rather than the use of autologous cells might be utilized for several obvious reasons, for example, the harvesting of autologous cells from a patient may be impractical or not possible. Moreover, the Examiner contends that methods of cultivating a graftable skin material comprising growing keratinocytes in the presence of autologous fibroblasts is well documented in the art. For example, Hansbrough *et al.* allegedly disclose a cultivated skin material comprising autologous fibroblasts co-cultured with keratinocytes in a collagen glycoaminoglycan matrix (citing page 2125-2126, Materials and Methods).

Hansbrough *et al.* describe seeding human dermal fibroblasts on the laminated collagen-glycosaminoglycan (GAG) and inoculating keratinocytes onto the porous, non-laminated Collagen-GAG. A large seeding density of keratinocytes (0.54 x106 to 1.0 x 106 cells/cm2) was required because there was no feeder layer of nonproliferating 3T3 cell in the model of Hansbrough *et al.* As discussed, *supra*, Della Valle *et al.* use 3T3 cells, but not human dermal fibroblasts as a feeder layer for the cultivation of keratinocytes on LaserskinTM. ***Della Valle et al. do not teach or suggest using allogenic or autologous fibroblasts in the method.*** Hence, Della Valle *et al.* clearly demonstrate the difference between the prior art and the presently claimed methods in growing keratincoytes on LaserskinTM.

The presently claimed methods are neither taught nor suggested by the prior art. Attempts have been made to grow the keratinocytes without the mouse 3T3 cells in order to minimize the xenogenic reaction. However, in the absence of the irradiated 3T3 cells, it is difficult

to grow the keratinocytes on any substratum. ***Hansbrough et al. do not teach or suggest a co-culture of autologous fibroblasts and keratinocytes.*** Rather, keratinocytes and dermal fibroblasts were grown in different layers of the collagen-GAG according to the teachings of Hansbrough *et al.* While dermal fibroblasts were seeded on the basal porous surface of the collagen-GAG, keratinocytes were plated on the upper laminated collagen-GAG. ***Hansbrough et al. do not teach or suggest an initial direct physical contact between the dermal fibroblasts and the keratinocytes.*** Without any feeder layer to enhance the growth of keratinocytes, a large seeding of keratinocytes was required, which was approximately 20 times more concentrate than the seeding density of keratinocytes in the present invention.

Further to the above explanations, Hansbrough *et al.* teach using autologous fibroblasts and keratinocytes in a collagen-glycosaminoglycan matrix. The nature and biocompatiblity of the substratum of the present invention such as Laserskin™ is very different from a collagen-glycosaminoglycan. Hansbrough *et al.* seeded dermal fibroblasts on the basal, porous side and keratinocytes on the upper, nonporous, laminated side. In contrast, according to the present invention, both the upper and basal sides are seeded with dermal fibroblasts.

Della Valle *et al.* in view of Cooper *et al.*, Hansbrough *et al.* and Meyers *et al.*

The Examiner rejects claims 4-6 and 11-13 under 35 U.S.C. 103(a) as being unpatentable over Della Valle *et al.* in view of Cooper *et al., J Invest Dermatol,* (1993) 110:811-819, Hansbrough *et al.* and Meyers *et al., J Burn Care Rehabil,* (1997) 18:214-22. Claims 4-6 are drawn to methods of cultivating a graftable skin said graftable skin comprising a biosynthetic substrates of benzyl-hyaluronic acid upon which keratinocytes and fibroblasts are grown. Claims 11-13 are drawn to graftable skin materials having apparently two sides comprising on a first side keratinocytes grown upon a layer of fibroblasts and on a second side only fibroblasts. The Examiner urges that an essential element of claims 4-6 is the co-culture of keratinocytes and fibroblast cells on a biosynthesis substrate. The limitations of claims 5 and 6 recite that the fibroblast are allogenic or autologous.

According to the Examiner, it is well known in the art that the presence of a dermal layer consisting in part of fibroblasts contributes to improved graft "take rates" (*citing* Cooper *et al.*) While Cooper *et al.* do not teach the use of a hyaluronic acid membrane, Cooper *et al.* teach that the inclusion of fibroblasts in graftable material increases the production of collagen in vitro, results in

the production of laminin at the appropriate dermoepidermal junction in vivo and improves the quality of the dermoepidermal junction compared to keratinocyte sheet grafts. Allegedly, these results are an extension of work published in Hansbrough *et al.* in which collagen aminoglycan membranes were used to autograft cultured fibroblasts and keratinocytes in burn patients.

The Examiner adds that Myers *et al.* teach using a hyaluronic acid membrane for the delivery of cultured keratinocytes. Allegedly, the method involves the culturing of autologous keratinocytes on a perforated hyaluronic membrane in the presence of irradiated, non-proliferating fibroblast cells, experiments described in Meyers *et al.* include the comparison of grafting in the presence or absence of a dermal layer, and dermal layers in wound areas were allegedly generated by autografting de-epidermalised dermis (which consists essentially of fibroblasts.) Allegedly, the data of Meyers *et al.* indicates that the best results were achieved with keratinocytes cultured on hyaluronic acid membranes and grafted onto wounds which contained a dermal layer, i.e. which had fibroblasts present. (*citing* Materials and Methods section, pages 215-218 and page 218, Table 2).

According to the Examiner, it would be readily apparent to one of skill in the art that a reasonable application of hylauronic acid membranes for grafting would incorporate the teachings of Cooper *et al.* (indicating that the co-culturing of live fibroblasts with keratinocytes in cultivated skin material provides advantages over keratinocytes alone and the teachings of Meyers *et al* which points to the need of fibroblast (dermal) cells for better graft formation). Allegedly, given the directionality of the dermo-epidermal junction it would be *prima facie* obvious to culture keratinocytes and fibroblasts as disclosed in claim 4 with one side of the membrane facing the developing dermis and consisting of fibroblasts and a second side of keratinocytes underlaid with fibroblasts. The Examiner maintains that culturing of keratinocytes over viable fibroblasts on one face of the membrane is an obvious extension of using 3T3 feeder cells.

Applicants respectfully disagree. The model of Cooper *et al.* is similar to the model taught by Hansbrough *et al.*, discussed above. Cooper *et al.* seeded keratinocytes on a laminated collagen-GAG (See, page 812, left column, first paragraph) and inoculated dermal fibroblasts on the porous, non-laminated collagen-GAG (See, page 812, right column, first paragraph). ***Cooper et al. do not teach or suggest seeding keratinocytes on a substratum according to the present invention such as Laserskin ™.***

Applicant submits that while Cooper *et al.* do teach that 'In skin substitutes,...the addition of viable fibroblasts....' did increase the take and that the added dermal fibroblasts

modulated the collagen-GAG to facilitate the take of the composite graft, ***according to Cooper et al., the keratinocytes seeded on the uppermost laminated surface were not in the same planar surface of pre-seeded dermal fibroblasts, whereas the keratinocytes and dermal fibroblasts according to the present invention are in the same plane.***

Applicant submits that while Meyers *et al.* generally describe 'culturing of keratinocytes on a perforated hyaluronic membrane in the presence of irradiated, non-proliferating fibroblasts cells...', ***Meyers et al. use irradiated, non-proliferating mouse 3T3 cells*** as was known in the art. In contrast, the present invention provides non-irradiated, proliferating human dermal fibroblasts. Such cells are biologically different from 3T3 cells. Regarding Meyers *et al.*'s statements that 'The dermal layers in wound...(which consists essentially of fibroblasts)', Applicant submits that this is not material to the present invention since ***such fibroblasts are involved in the in vivo regeneration of the dermal layer.*** Such fibroblasts directly originate from the recipient wound bed. Meyers *et al.* do not teach or suggest adding cultured dermal fibroblasts, and there is no reasonable expectation that such cultured dermal fibroblasts could be added successfully.

The Examiner alleges that application of hylauronic acid membranes for grafting would incorporate the teachings of Cooper *et al.* (indicating co-culturing live fibroblasts with keratinocytes in cultivated skin material). Applicants submit that those of ordinary skill in the art working in skin culture and burn surgery understand the drawbacks of utilizing mouse 3T3 cells as feeder layer for the fabrication of cultured skin grafts. However, it is difficult to ensure a rapid in vitro multiplication of keratinocytes without 3T3 cells. ***Prior to the present invention, no one had replaced 3T3 cells with non-irradiated, proliferating human fibroblasts. Moreover, there was no reasonable expectation that irradiated, nonproliferating, xenogenic 3T3 cells could be successfully replaced with non-irradiated, proliferating human fibroblasts.***

Della Valle *et al.* in view of Rennenkampf *et al.*

The Examiner rejects claim 7 under 35 U.S.C. 103(a) as unpatentable over Della Valle *et al.* further in view of Rennenkampf *et al.*, *Surgery* (1996) 120:16-22. According to the Examiner, Della Valle *et al.* teach using hyaluronic membranes for growing keratinocytes. The method of Della Valle *et al.* utilized a feeder layer of irradiated 3T3 fibroblast cells. The Examiner contends that Rennekampf *et al.* teach the growth of keratinocytes in the absence of fibroblast feeder cells. (citing page 17 2nd col). According to the Examiner, one of skill in the art could clearly apply

the technique of Rennekampf *et al.* to culturing keratinocytes on hyaluronic membranes with a reasonable chance of success. Motivation for combining the techniques can allegedly be found in situations in which 3T3 cells are too immunogenic for engraftment techniques.

Applicants submit that Rennekampf *et al.* report engraftment of ***cultured keratinocytes*** (*see*, page 10, first paragraph). This is completely different from the methods of the present invention. Rennenkampf *et al.* prepare an epidermal equivalent by cultivating a pure confluent keratinocyte sheet on a plain synthetic hydrophilic dressing (Hydroderm) (*see*, page 17, left column, last sentence). The hydrophilic dressing (Hydroderm) comprising cultured keratinocytes was then placed on top of a dermal equivalent (Dermagraft) (*see*, page 18, left column, line 14) which consists of living fibroblasts. In contrast, according to the present invention, the epidermal equivalent is fabricated with keratinocytes and living dermal fibroblasts on a substratum such as LaserskinTM.

Orgill *et al.*, Zacchi *et al.*, Meyers *et al.*, Della Valle *et al.* and Hansbrough *et al.*

The Examiner rejects claims 15-17 under 35 U.S.C. 103(a) as unpatentable over Orgill *et al.*, U.S. Patent 5,489,304, Zacchi *et al.*, *J Biomed Mater Res* (May 1998) 40:187-194, Meyers *et al.*, *J Burn Care Rehabil* (1997) 18:214-22, Della Valle *et al.* and Hansbrough *et al.* Claims 15-17 are drawn to a method of grafting a skin material involving using a layer of collagen-glycoaminoglycan and applying a biosynthetic substratum comprising at least a layer of keratinocytes.

According to the Examiner, Orgill *et al.* teach using a collagen glycosaminoglycan matrix (CG-matrix) for generating a dermal layer in patients suffering from burn injuries. The method of Orgill *et al.* involves generating a "neodermis" facilitated by the placement of a CG-matrix followed by engrafting a subsequent layer of cultured epithelial cells (CEA – comprising keratinocytes). (citing column 4, line 9- column 6, line 26) The Examiner admits that Orgill *et al.* do not teach using cultured keratinocytes supported by a biosynthetic substratum.

According to the Examiner, Zacchi *et al.* teach using hyaluronic acid substrates for cultivating fibroblasts and keratinocytes. Moreover, according to the Examiner, they indicate that using keratinocytes on a support, such as a hyaluronic acid membrane, is beneficial in the grafting of keratinocytes. The Examiner admits that Zacchi *et al.* does not teach two step grafting techniques in which a neodermis is initially formed.

According to the Examiner, Myers *et al.* teach using a hyaluronic acid membrane for the delivery of cultured keratinocytes. The results of Meyers *et al.* allegedly indicate that the best results were achieved with keratinocytes cultured on hyaluronic acid membranes and grafted onto wounds which contained a dermal layer (citing page 218, Table 2). The Examiner admits that Meyers *et al.* do not teach the generation of a dermal wound bed using a collagen- glycoaminoglycan matrix.

The Examiner maintains that it would be *prima facie* obvious to one of skill in the art to combine the teaching of Orgill *et al.* regarding the use of an artificial dermis (comprising *e.g* Integra) with the teachings of Zacchi *et al.* and Meyers *et al.* concerning the use of a hyaluronic supporting membrane and the need for an adequate dermal wound bed. Allegedly, the teachings of Della Valle *et al.* and Hansbrough *et al.* point to the obviousness of co-culturing fibroblasts and keratinocytes on hyaluronic acid membrane and further the use of autologous fibroblasts and keratinocytes in co-cultures on a biosynthetic substratum.

As explained above, Meyers *et al.* teach using a hyaluronic acid membrane in the presence of irradiated 3T3 cells, but they do not teach or suggest proliferating human dermal fibroblasts as in the present invention. Hence, Meyers *et al.* do not teach or suggest co-culturing keratinocytes and human dermal fibroblasts.

Applicants submit that Orgill *et al.* report the direct seeding of keratinocytes onto a collagen-GAG by gentle centrifugation (500 rpm for 15 min at 4oC). Hence, Orgill *et al.* do not teach or suggest co-culturing keratinocytes and human dermal fibroblasts. Orgill *et al.* teach a completely different methodology of keratinocyte cultivation from that of the present invention.

Applicants submit that Zacchi *et al.* teach using hyaluronic acid for the cultivation of fibroblasts and keratinocytes. Zacchi *et al.* grow dermal fibroblasts on HyaffTM and applied as dermal equivalent. Zacchi *et al.* do not teach or suggest co-culturing keratinocytes and human dermal fibroblasts.

In order for an invention to be prima facie obvious over a combination of references, the references as combined must teach every element of the claimed subject matter. Moreover, there must be some reasonable expectation of success from combining the references. Applicants respectfully submit that the present invention is not *prima facie* obvious over the references cited. It was well addressed that the engraftment of cultured skin substitutes consisting of autologous keratinocytes onto the neodermis was inconsistent. The prior art does not teach or suggest applying

cultured keratinocytes cultivated on a substratum such as LaserskinTM or a hyaluronic derivative with IntegraTM. Combining cultured LaserskinTM as an epidermal equivalent with IntegraTM was cited as a further novel approach in a recent publication "Clinical evaluation of skin substituted" (See, Kearny *et al.*, Burn 2001; 27: 545-551).

Applicants respectfully disagree with the Examiner's statement that "The teachings of Della Valle *et al.* and Hansbrough *et al.* point the obviousness of co-culturing fibroblasts...on a biosynthetic substratum." Respectfully, the prior art does not teach or suggest using human dermal fibroblasts as a feeder layer for cultivation of keratinocytes or replacing mouse 3T3 cells with human dermal fibroblasts.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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PATENT

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Claim 1 has been amended as follows:

1. (Amended) A method for [cultivation of] cultivating graftable skin comprising:
growing a layer of dermal fibroblasts upon [at least] an upper side of a biosynthetic substratum of [a derivative of benzyl] an esterified hyaluronic acid; and, after said dermal fibroblast layer [becomes at least sub-confluent] begins to proliferate, growing a layer of keratinocytes over said dermal fibroblasts upon said upper side of said substratum to form a composite skin graft material, said keratinocytes being harvested from a target donor patient.

Claim 2 has been amended as follows:

2. (Amended) The method according to claim 1 wherein said dermal fibroblasts are allogenic to the keratinocytes.

Claim 3 has been amended as follows:

3. (Amended) The method according to claim 1 wherein said dermal fibroblasts are autologous to the keratinocytes.

Claim 4 has been amended as follows:

4. (Amended) A method for [cultivation of] cultivating graftable skin comprising:
growing a first layer of dermal fibroblasts upon a [first] basal side of a biosynthetic substratum of [a derivative of benzyl] an esterified hyaluronic acid;
growing a second layer of dermal fibroblasts upon [a second] an upper side of said biosynthetic substratum; and
after said second dermal fibroblast layer [becomes at least sub-confluent] begins to proliferate, growing a layer of keratinocytes over said dermal fibroblasts upon said upper side of said substratum to form a composite skin material, said keratinocytes having been harvested from a target donor patient.

Claim 5 has been amended as follows:

5. (Amended) The method according to claim 4 wherein said dermal fibroblasts are allogenic to the keratinocytes.

Claim 6 has been amended as follows:

6. (Amended) The method according to claim 4 wherein said dermal fibroblasts are autologous to the keratinocytes.

Claim 7 has been amended as follows:

7. (Amended) A method for [cultivation of] cultivating graftable skin comprising:
growing a layer of keratinocytes upon an upper side of a substratum of a biosynthetic substratum of [a derivative of benzyl] an esterified hyaluronic acid to form a composite skin graft material, said keratinocytes having been harvested from a target donor patient.

Claim 8 has been amended as follows:

8. (Amended) A graftable skin material compromising a composite of:
a biosynthetic substratum of [a derivative of benzyl] an esterified hyaluronic acid;
a layer of dermal fibroblasts upon [at least] an upper side of said biosynthetic substratum; and
a layer of keratinocytes over said dermal fibroblasts upon said upper side of said substratum, said keratinocytes having been harvested from a target donor patient.

Claim 9 has been amended as follows:

9. (Amended) The material according to claim 8 wherein said dermal fibroblasts are allogenic to the keratinocytes.

Claim 10 has been amended as follows:

10. (Amended) The material according to claim 8 wherein said dermal fibroblasts are autologous to the keratinocytes.

Claim 11 has been amended as follows:

11. (Amended) A graftable skin material comprising a composite of:
a biosynthetic substratum of [a derivative of benzyl] an esterified hyaluronic acid;
a first layer of dermal fibroblasts upon a [first] basal side of said biosynthetic substratum;
a second layer of dermal fibroblasts upon a [second] upper side of said biosynthetic substratum; and
a layer of keratinocytes over said dermal fibroblasts upon said upper side of said substratum, said keratinocytes having been harvested from a target donor patient.

Claim 12 has been amended as follows:

12. (Amended) The material according to claim 11 wherein said dermal fibroblasts are allogenic to the keratinocytes.

Claim 13 has been amended as follows:

13. (Amended) The material according to claim 11 wherein said dermal fibroblasts are autologous to the keratinocytes.

Claim 14 has been amended as follows:

14. (Amended) A graftable skin material comprising:

a substratum of a biosynthetic substratum of [a derivative of benzyl] an esterified hyaluronic acid; and
a layer of keratinocytes upon an upper side of said substratum, said keratinocytes having been harvested from a target donor patient.

Claim 15 has been amended as follows:

15. (Amended) A method for grafting a graftable skin material comprising the steps of:
applying an artificial skin substrate upon a wound bed of a recipient patient; said artificial skin substrate comprising a layer of collagen-glycoaminoglycan on a basal side to be juxtaposed to said wound bed and a covering membrane of silicone on an opposing upper side;
allowing a [sufficient time to form] a vascularized wound bed to form under said collagen-glycoaminoglycan; [thereupon]
removing said silicone membrane; and [thereupon]
applying a basal side of a sheet of cultivated skin material over said collagen- glycoaminoglycan, said cultivated skin material comprising [at least] a layer of keratinocytes upon an upper side of a substratum, said keratinocytes being harvested from a target donor patient.

Claim 16 has been amended as follows:

16. (Amended) The method according to claim 15 wherein said cultivated skin material further comprises a layer of dermal fibroblasts upon [at least] an upper side of a biosynthetic substratum and wherein said layer of keratinocytes is over said dermal fibroblasts.